

No. 22-56014

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

UNITED STATES OF AMERICA,

Plaintiff-Appellant,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., a California
corporation; CELL SURGICAL NETWORK CORPORATION, a California
corporation; ELLIOT B. LANDER, M.D., individual; MARK BERMAN, M.D.,
individual,

Defendants-Appellees.

On Appeal from the United States District Court
for the Central District of California

REPLY BRIEF

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INTRODUCTION AND SUMMARY

Defendants create and market biological products that are primarily made of what they call “stromal vascular fraction” or “SVF.” Defendants claim that SVF is a cure-all substance—what one defendant called “liquid magic”—treating everything from stroke to macular degeneration to erectile dysfunction. Depending on the illness at issue, defendants drip their SVF products into people’s veins, inject the SVF products into patients’ joint spaces, and have even administered these SVF products into patients’ brains and eyes. Defendants are wrong to urge that, unlike other doctors and scientists who create and use cellular therapies, they—and the SVF products they create and tout—are entirely exempt from FDA regulation.

Defendants ask this Court to reject the conclusions of the D.C. Circuit and Eleventh Circuit that products of this type are “drugs” under the Federal Food, Drug, and Cosmetic Act’s (FDCA) statutory definition. Defendants concede that their SVF products satisfy the plain text of that statutory definition and that they are asking this Court to create an “atextual” exception. No sound basis exists for deviating from the statute’s unambiguous terms. The Supreme Court has rejected a similar invitation. And contrary to defendants’ contention, FDA’s regulation of the SVF products that defendants market as cure-alls for various diseases is not “absurd.” To the contrary, it perfectly fits the purposes of the FDCA and, indeed, a recent amendment to the FDCA presupposes that products of this type are drugs.

Defendants' manufacturing of SVF further illustrates that FDA is regulating a product rather than a medical procedure. SVF does not exist anywhere in the body. Defendants create it from adipose tissue through an extensive process, sometimes in their own clinics while patients sit in a waiting room and other times in a laboratory on the other side of the country. That is the production of a drug, and it is properly regulated as such. Refusing to create an atextual exception in this case does not implicate defendants' broader arguments about applying the FDCA to surgical procedures such as skin grafts; to the contrary, FDA has long excepted such matters from regulation.

Defendants' problem is not that FDA is seeking to regulate surgical procedures but rather that defendants do not qualify for the relevant regulatory exception, which only applies to an establishment that "removes [human cells, tissues, and cellular and tissue-based products (HCT/P's)] from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). As the Eleventh Circuit has explained, clinics like defendants' businesses remove adipose tissue and then implant SVF and therefore do not implant "such" HCT/P.

Defendants acknowledge that they remove adipose tissue, that adipose tissue is an HCT/P, and that the SVF that they implant is not adipose tissue. The fact that defendants remove, embedded within the adipose tissue, each of the individual cells that end up in the final SVF products they create does not entitle them to rely on the exception. The exception's text is not naturally read to apply to procedures that remove

one HCT/P and implant a different HCT/P merely because some subset of each HCT/P remains the same. And defendants’ reading also cannot be reconciled with the regulatory context, the provision’s history, and FDA’s longstanding interpretation of its own regulation.

ARGUMENT

I. Defendants’ SVF Products Are Drugs Under The Statutory Definition

A. Under the Federal Food, Drug, and Cosmetic Act, drugs cannot generally be marketed unless FDA has first determined that they are safe and effective for their intended use, *see* 21 U.S.C. § 355(a), and cannot, in any event, be adulterated or misbranded or be marketed if they are adulterated or misbranded, *see id.* § 331(a), (k). The statute defines the term “drug” to include, as relevant here, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals,” articles “intended to affect the structure or any function of the body,” and any components of such articles. *Id.* § 321(g)(1)(B)-(D).

At issue here are products that defendants refer to as comprising “stromal vascular fraction,” or “SVF,” which defendants tout as having healing properties when it is injected into patients, Gov. Br. 11, 21—going so far as to call it “liquid magic,” 7-ER-1060; *see* 7-ER-1060-1065; *see also, e.g.*, 10-ER-1373 (touting the “therapeutic benefits of SVF” and its use “for various degenerative conditions”). Because SVF is intended to cure or treat disease, and to do so by affecting the function of the body, it

satisfies the statutory definition of “drug” twice over. Gov. Br. 21-25; *see United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014); *see also United States v. U.S. Stem Cell Clinic, LLC*, 998 F.3d 1302, 1305-1306 (11th Cir. 2021) (explaining why a “body-fat-derived” stem-cell product like the ones at issue in this case qualifies as a drug).

Defendants do not dispute that the plain terms of the statutory definition of drug enacted by Congress encompasses their SVF products. Instead, they ask this Court to adopt an “atextual” approach, Br. 33, urging that “the statute’s ‘purpose’ must take precedence over ‘the literal words.’” Br. 28 (quoting *United States v. American Trucking Ass’n*s, 310 U.S. 534, 543 (1940)). This argument fails at every level.

Far from leading to “absurd results,” Br. 28, applying the FDCA to defendants’ so-called “liquid magic” fits the Act’s purposes like a glove. As the Supreme Court has explained, “Congress fully intended that the Act’s coverage be as broad as its literal language indicates.” *United States v. Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969); *see id.* at 790-791, 793 (rejecting a court of appeals’ decision to disregard the definition of “drug” based on that court’s view of what Congress “intend[ed]” or what would be “contrary to common sense”). In particular, Congress sought to combat untested assertions that products would cure diseases. *See id.* at 797 (“There are hundreds of worthless contrivances being sold to and used by gullible people.” (quoting 80 Cong. Rec. 10,236 (1936) (statement of Rep. Chapman))). And Congress added the “pre-market clearance provisions,” which prohibit the marketing of drugs unless FDA

has concluded ahead of time that they are safe and effective, in response to an incident “where nearly 100 persons died as the result of consuming an untested drug.” *Id.* at 797-798, 798 n.17; see *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 612-613 (1973) (describing the original premarket review for safety and 1962 amendment requiring premarket review for efficacy). There is nothing “absurd,” Br. 28, about applying this scheme to ensure that defendants cannot market their products as treating or curing a wide range of diseases without first demonstrating to FDA that the products are safe and effective for those intended uses, and further prohibiting defendants from marketing adulterated or misbranded versions of those products. That is all the more clear when interpreting a statute that “is to be given a liberal construction,” *Article of Drug . . . Bacto-Unidisk*, 394 U.S. at 798, and read “broadly in order to protect public health,” *United States v. Kaplan*, 836 F.3d 1199, 1208 (9th Cir. 2016); see *id.* at 1210 (describing “Congress’s intent that the FDCA be interpreted broadly”).

Defendants seek to escape the statute’s language largely by describing their use of SVF as “surgery” and arguing that the FDCA does not regulate medical procedures. But this case is not about regulating a medical procedure; rather, this case is about regulating a product. This Court explained the difference in *United States v. Kaplan*, 836 F.3d 1199, which held that a doctor could be held liable under the FDCA for conducting biopsy procedures with a reused “needle guide” that was only intended for a single use. In rejecting the doctor’s argument that its holding “impermissibly interferes with a physician’s ability to treat patients,” the Court distinguished between

regulating a product used in a medical procedure and regulating the procedure itself. *Id.* at 1210. The Court relied, in particular, on the D.C. Circuit’s decision in *United States v. Regenerative Sciences*, 741 F.3d 1314, which concerned a stem-cell product (there referred to as a stem-cell “Mixture”) similar to the one at issue here. *Kaplan*, 836 F.3d at 1210. This Court agreed with the D.C. Circuit’s reasoning that FDA was not regulating a medical procedure: “FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe.” *Id.* (quoting *Regenerative Scis.*, 741 F.3d at 1319).

Defendants disagree with the D.C. Circuit’s discussion of this issue, *see* Br. 40-41, without acknowledging that this Court has already accepted it. And the reasoning is, in any event, correct. FDA regulates all manner of drugs and devices that are used in medical procedures; this has never been equated with regulating the procedures themselves. Thus, there is no serious dispute that FDA regulates the drugs used by an anesthesiologist and the scalpels, gauze, and other equipment used by a surgeon, even though regulation of these articles places constraints on doctors’ performance of surgery.

The facts of this case further illustrate that FDA is regulating a product rather than a medical procedure. The processing steps to manufacture SVF after removing the patient’s adipose tissue do not resemble anything that even today—let alone when Congress passed the FDCA in 1938—would naturally be described as “surgery.” Rather, they reflect the process of manufacturing a drug product. By defendants’ own

account, they create a “soup” comprising various types of cells, platelets, and growth factors, all of which are normally dispersed throughout adipose tissue. FER-94-95; *see, e.g.*, 6-ER-756-757; 7-ER-1054; 8-ER-1252-1253; 10-ER-1382. Defendants create that “soup” through an extensive process of exposing the patient’s tissue to enzymes that break it down—a process that one expert witness analogized to “unleashing” a “brood of termites” on a wood dowel, 6-ER-720—and then using high-speed “centrifugation,” “washing,” and filtration. *See* Gov. Br. 8-10, 27; *see, e.g.*, FER-94-95; 6-ER-701; 6-ER-712-713; 7-ER-1033-1034; 9-ER-1339; 9-ER-1344-1345. In some cases, defendants (acting through a contract laboratory), also “expand” that soup by “select[ing]” and then “grow[ing]” cells “in culture.” 9-ER-1339; 9-ER-1344-1345; *see* 3-ER-175-176; 4-ER-325-327; 7-ER-1033-1034; 7-ER-1052-1053. An interview with defendants notes that “SVF” is “not pure stem cells” and states: “We produce SVF (over 40 ingredients and can’t be characterized)” FER-115-116. And defendants’ marketing confirms that they are manufacturing and selling a product, touting their “technology to produce a solution rich with your own stem cells,” FER-53 (defendants’ brochure), and marketing SVF to “[p]atients who are looking for non-surgical alternatives to their degenerative disorders,” 10-ER-1378 (defendants’ website).

The error in defendants’ legal theory is highlighted by its application to what they refer to as the “expanded MSC” treatment. In that process, after a patient’s adipose tissue is removed, it is “sent in a sterile transport system” to a contract “lab.” 9-ER-1344; *see, e.g.*, FER-79. Although the patient is in California, defendants have used labs

in New Jersey and Florida. 4-ER-306-307; 4-ER-424; 9-ER-1339; 9-ER-1345-1347; FER-11; *see* 4-ER-363; 7-ER-1052-1053; FER-79. There is no merit to defendants’ characterization as “surgery” of a laboratory technician’s creation of a product that will be injected into a patient on the other side of the country. And defendants rightly make no effort to draw any legal distinction between the product created in a laboratory and the product created when they engage in what their own witness described as a “somewhat similar” process in their clinics. 9-ER-1344. The production of SVF in their clinics is similarly not part of any surgical procedure; to the contrary, after the adipose tissue is removed, the patient typically sits in the waiting room while the SVF is produced. 3-ER-214-215. Defendants cannot escape FDA regulation of a drug merely by manufacturing it in a clinic instead of in a sterile laboratory.

Such manufacturing of a drug, regardless of where it takes place, bears no resemblance to the surgeries to which defendants seek to analogize their conduct. *See* Br. 28-30 (discussing bypass surgeries and hair transplants); *see also* 9-ER-1320-1322 (one defendant acknowledging the differences between the creation of SVF products and using a fat graft to plug a skull leak). FDA has not endeavored to regulate the use of a patient’s own cells and tissues in those types of surgeries; to the contrary, its regulations exempt them entirely from FDA rules governing HCT/P’s. *See* 21 C.F.R. § 1271.15(b). Defendants’ contention that FDA has overstepped its bounds by regulating the practice of medicine is thus entirely without merit. Even if there were an atextual limitation on the term “drug” to accommodate some narrow circumstances

that bear none of the hallmarks of drug manufacturing and all of the hallmarks of surgery, such a limit would have no application in this case. Nor would it matter in any other case since FDA regulations preclude enforcement in the context of such surgical procedures.

For similar reasons, defendants are wrong to suggest that there is something novel about FDA's approach that would counsel against reading the statute as it is written. FDA did not "suddenly . . . claim[] to have jurisdiction" over drug products involving human cells and tissues in 1997. Br. 46. What was new at the time was the agency's comprehensive framework to govern the regulation of such products, since the regulation had previously been "highly fragmented." FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* 6 (Feb. 28, 1997), <https://perma.cc/M2QS-PPNC> (1997 Proposed Approach); *see, e.g.*, 58 Fed. Reg. 65,514, 65,514, 65,516 (Dec. 14, 1993) (noting FDA regulation of certain "tissues," "[s]omatic cell therapy," and "gene therapy," including "as drugs, biological products, or medical devices," and explaining that regulation often occurred "on a case-by-case basis"); 58 Fed. Reg. 53,248 (Oct. 14, 1993) (similar). It was necessary not because FDA was regulating in a new area but because the development of "new techniques" made it appropriate to establish and formalize a "unified" regulatory approach. 1997 Proposed Approach 6. What would be novel would be defendants' proposal to eliminate entirely a category of drug products from FDA's oversight, over FDA's objection and without any basis in the statutory text for doing so. *Cf. Article of Drug . . . Bacto-Unidisk*, 394 U.S. at 791-792

(stressing that FDA is the “expert agency charged with the enforcement of remedial legislation”); *United States v. Sullivan*, 332 U.S. 689, 694 (1948) (stressing that FDA has “broad discretion” to “perform [its] duties fairly without wasting [its] efforts” unnecessarily).

Recent legislation confirms that Congress presumed that products like defendants’ would require FDA approval. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133, 143 (2000) (interpreting the terms “drug” and “device” in light of “subsequent statutes” that “more specifically address the topic at hand”). As noted in the opening brief (Gov. Br. 22), in the 21st Century Cures Act, Congress amended a section of the FDCA governing “Expedited approval of drugs” by adding a provision for “regenerative medicine therap[ies],” including “cell therap[ies]” and “human cell and tissue products.” 21 U.S.C. § 356(g)(8); *see* Pub. L. No. 114-255, div. A, tit. III, subtit. D, § 3033(a), 130 Stat. 1033, 1101-1103 (2016). The provision’s proponents explained that it would provide a “faster approval process” for “using” people’s “own stem cells.” 162 Cong. Rec. S6693 (daily ed. Dec. 5, 2016) (statement of Sen. Kirk); *see* 162 Cong. Rec. S6793 (daily ed. Dec. 7, 2016) (statement of Sen. Alexander); *see also Continuing America’s Leadership: The Future of Medical Innovation for Patients: Hearing Before the S. Comm. on Health, Educ., Labor, & Pensions*, 114th Cong., 1st Sess. 2 (2015) (statement of Sen. Alexander) (“We want to make sure that FDA is ready for the developments coming, such as . . . regenerative adult stem cell therapies derived and put back into the same patient”); *cf.* Pub. L. No. 114-255, div. A, tit. I, § 1001(b)(4)(D), 130 Stat. at 1041

(appropriating funds for “clinical research to further the field of regenerative medicine using adult stem cells, including autologous [from the same person] stem cells”). Defendants make no attempt to reconcile this recent congressional action to streamline the drug approval process for products used in modern regenerative cell therapies with their view that it would be “absurd” to treat such products as subject to FDA approval in the first place.

Nor do defendants identify any statutory basis for—or really attempt to defend—the district court’s conclusion that defendants’ products are not drugs because “[t]hey are not fungible goods that can be sold, mass produced, or patented.” 1-ER-18. Defendants do argue that FDA regulation is inappropriate because FDA’s regulations were designed for mass-produced drugs, rather than individualized treatments for particular patients. Br. 30. But the statute does not limit FDA’s regulatory authority in this way. FDA routinely reviews and has approved applications for customized therapies where a single batch of product is created for an individual patient, some through a manual process. Such products include autologous (from the same person) cell-based therapies used to treat lymphoma,¹ prostate cancer,² a red blood cell disorder,³ and even the appearance of wrinkles⁴; cord-blood derived stem cells used for

¹ See FDA, *YESCARTA (axicabtagene cilolencel)* (Nov. 4, 2022), <https://perma.cc/L9PR-BR7Q>.

² See FDA, *PROVENGE (sipuleucel-T)* (May 28, 2019), <https://perma.cc/8TY4-XYBV>.

³ See FDA, *ZYNTEGLO* (Sept. 19, 2022), <https://perma.cc/W85X-932X>.

⁴ See FDA, *LAVIV* (Mar. 16, 2018), <https://perma.cc/9JHE-V8ZT>.

patients with blood cancers⁵; and individualized fecal transplants used to prevent recurring infections.⁶ *See also* 3-ER-138-141 (noting that FDA has received “regulatory submissions” and has pending “Investigational New Drug Applications” for “adipose tissue-derived cellular treatments”); 5-ER-574-579 (explaining that “autologous products made specifically for individual people” can be made to meet “certain standards” and have “certain characteristics” and that “SVF can be produced with consistent strength, quantity, and purity”). Congress gave no indication that it intended to exclude customized treatments from the requirement that manufacturers demonstrate that drugs are safe and effective before they are administered to patients. And defendants offer no response to the observation that “the Act applies even to drugs made on an individual basis, such as drugs that are ‘compounded’ by a pharmacy or physician ‘for an identified individual patient.’” Gov. Br. 25 (quoting 21 U.S.C. § 353a).

In short, although defendants couch their arguments in terms of an exception for surgical procedures, they seek something quite different: an exception from the FDCA’s comprehensive regulation of products marketed to treat disease for products that were derived in part from the patient’s own cells or tissues. But defendants properly concede that the FDCA’s text contains no such exception. And as discussed, applying the FDCA’s text as written aligns with the statute’s purposes, creates no

⁵ *See* FDA, *OMISIRGE* (May 16, 2023), <https://perma.cc/2MA7-MZ5J>.

⁶ *See* FDA, *REBYOTA* (Dec. 19, 2022), <https://perma.cc/9G7S-2ZHQ>.

absurdity, and indeed has recently been contemplated by Congress. Defendants’ arguments thus run headlong into the longstanding principle that “when the statute’s language is plain, the sole function of the courts—at least where the disposition required by the text is not absurd—is to enforce it according to its terms.” *Lamie v. U.S. Tr.*, 540 U.S. 526, 534 (2004).

B. Defendants’ effort to obtain a judicial re-writing of the statute by relying on the major-questions doctrine only underscores the absence of any support for their position. This case does not involve a decision of vast “economic and political significance” or an assertion of “extravagant statutory power over the national economy.” *West Virginia v. EPA*, 142 S. Ct. 2587, 2608-2609 (2022) (cited at Br. 33, 37, 41, 42, 44, 45, 48); *cf. id.* at 2604 (an “aggressive transformation in the domestic energy industry”); *Biden v. Nebraska*, 143 S. Ct. 2355, 2373-2375 (2023) (providing “monetary benefits” to “[p]ractically every student borrower” in the country at a cost of between \$469 billion and \$519 billion); *National Fed’n of Indep. Bus. v. Occupational Safety & Health Admin.*, 142 S. Ct. 661, 665 (2022) (per curiam) (“order[ing] 84 million Americans to either obtain a COVID-19 vaccine or undergo weekly medical testing at their own expense”); *Alabama Ass’n of Realtors v. Dep’t of Health & Human Servs.*, 141 S. Ct. 2485, 2489 (2021) (per curiam) (halting the potential eviction of “[a]t least 80% of the country” with an estimated “economic impact” of “\$50 billion”). Nor is FDA straying beyond its customary regulatory role of ensuring that drugs that are marketed as treatments or cures for disease are safe and effective for their intended uses. Nor is

FDA intruding on state law; the whole point of the FDCA is to establish a “comprehensive, uniform regulatory scheme” for drugs and other specified products, even though FDA regulation may overlap with state regulation. *Regenerative Scis.*, 741 F.3d at 1319; *see also Wyeth v. Levine*, 555 U.S. 555, 566 (2009) (explaining that the FDCA protects people from the risks of “unsafe drugs and fraudulent marketing” and accordingly “supplement[s] the protection for consumers already provided by state regulation”).

FDA v. Brown & Williamson Tobacco, 529 U.S. 120, which defendants cite throughout their brief, further underscores the point. That is the canonical case applying what is now called the major-questions doctrine to the FDCA. There, the Supreme Court held that cigarettes and smokeless tobacco products as customarily marketed were not drugs and devices under the FDCA. *Id.* at 127. Each step of the Court’s analysis in that case runs counter to defendants’ argument here. The Court reasoned in *Brown & Williamson* that regulation of tobacco products as drugs or devices would be at odds with other FDCA provisions that require review for safety and efficacy—standards that do not fit tobacco. 529 U.S. at 134-139, 140-142. Here, by contrast, the premise of defendants’ treatments is that their SVF products are safe and effective for their intended uses; defendants merely seek to research and market these drugs without following the steps and meeting the standards applicable to all other drug products. In *Brown & Williamson*, the Court reasoned that despite “the economic and political significance of the tobacco industry at the time,” there was “no evidence” that

Congress “even considered the applicability of the Act to tobacco products,” and Congress had the “specific intent” not to regulate tobacco. *Id.* at 146-148. This case, by contrast, involves the application of the FDCA to products that did not even exist when the statute was first enacted. In *Brown & Williamson*, the Court stressed that FDA had repeatedly and expressly “informed Congress” that it lacked the authority to regulate tobacco and Congress then enacted “tobacco-specific legislation” “premise[d]” on the understanding that tobacco was not a drug or device. *Id.* at 143-146, 148-158. Here, by contrast, the relevant legislation confirms that Congress shares the view that products like defendants’ SVF products are drugs subject to FDA regulation and approval. Finally, in *Brown & Williamson*, the Court read the FDCA in light of tobacco’s “unique political history” and “significant” role in “the American economy.” *Id.* at 159-160. Here, emerging cellular therapies are unknown to most people and do not share tobacco’s “unique” history or vast “economic and political significance,” *id.* The rationale of *Brown & Williamson* thus does not extend to defendants’ SVF products. Rather, each of the Supreme Court’s considerations in that case confirms that SVF products are “drugs” within the meaning of the FDCA.⁷

⁷ In a footnote, defendants suggest that the district court’s judgment can be affirmed based on the court’s statement that there was “no evidence that Defendants adulterated or mislabeled any material in connection with the Expanded MSC Surgical Procedure.” Br. 50 n.4. Even if this footnote were adequate to raise the argument, *but see City of Portland v. United States*, 969 F.3d 1020, 1052 (9th Cir. 2020), it would provide no basis for affirming the judgment. The district court had no occasion to opine on whether defendants’ SVF products are adulterated or misbranded—having concluded

Continued on next page.

II. Defendants' SVF Product Is Not Entirely Excepted From FDA Regulation Under The Same Surgical Procedure Exception

Defendants have also not met their burden of establishing that they are entirely excepted from regulation under 21 C.F.R. § 1271.15(b), which provides that an “establishment that removes HCT/P’s from an individual and implants such HCT/P’s into the same individual during the same surgical procedure” is excepted from FDA regulation. *See* Gov. Br. 26-41; *U.S. Stem Cell Clinic*, 998 F.3d at 1309-1310. Defendants remove adipose tissue and implant SVF. That does not constitute removing an HCT/P and then implanting “such” HCT/P, but instead constitutes removing an HCT/P and then implanting a different HCT/P.

A. 1. Defendants agree that they remove adipose tissue from patients and that adipose tissue is an HCT/P. Br. 52. And they do not contend that the SVF that they subsequently implant into the patient is “such HCT/P.” Instead, they urge that none of that matters because certain cells are a component of both the adipose tissue and the SVF. According to defendants, the exception applies if they “reimplant *either* ‘such’

instead that no such requirements applied, 1-ER-13; 1-ER-18-19—and its apparent statement that the various inputs to SVF were not adulterated or misbranded has no particular relevance. *See* 1-ER-10-11 (citing lack of evidence “that Defendants label or mislabel *any material regulated by the FDA* in connection with the Expanded MSC Surgical Procedure” (emphasis added)). Additionally, any suggestion that the government did not present evidence that the “expanded” SVF product is adulterated and misbranded would be plainly contradicted by the record, which includes not only evidence that all of defendants’ SVF products are adulterated and misbranded, *see generally* 1-SER-87-94, but also evidence specific to the “expanded” product, *see, e.g.*, 10-ER-1443; 10-ER-1460; FER-14; FER-22-23; FER-56-57; FER-80.

adipose tissue *or* ‘such’ cells contained in the adipose tissue back into the patient.”

Br. 53. That interpretation is fundamentally misguided.

Even on its own terms, no sound basis exists for defendants’ apparent view that any HCT/P administered to a patient that comprises cells that came from the patient is entirely exempt from FDA regulation. The exception applies only insofar as an establishment “removes HCT/P’s from an individual and implants such HCT/P’s into the same individual.” 21 C.F.R. § 1271.15(b). Here, defendants implant an HCT/P (SVF) that they did not remove from the patient. Context confirms this natural reading of the text: it would have been very odd for FDA to exempt from all regulation drug products that are concededly different from what was removed from the patient merely because those products happen to include cells that were removed from the patient.

Indeed, defendants’ position has virtually no limiting principle and would mean that so long as they create and implant a product in a patient that comprises cells or other component parts taken from that patient (and they do so in one extended procedure), FDA has entirely excepted them from regulation, regardless of whether the resulting article bears any resemblance to the tissue that was removed. In defendants’ view, the only limits appear to be that the exception does not apply when doctors implant cells that never came from a patient at all—such as in a “donated organ” (Br. 54)—and when there is a “manufacturing process” that “alter[s] a patient’s cells biologically” (Br. 26-27), such as “[a]rguably” if doctors implant cells after they have “spliced the DNA,” Br. 54.

Defendants also ignore their significant manipulation of the adipose tissue once it is removed and instead attempt to apply the exception as if they merely implanted individual cells that they had isolated from that tissue. But as discussed, the SVF that is ultimately implanted into the patient does not exist anywhere in the human body; rather, it is created by defendants through an extensive process. Removing an HCT/P and then creating a different HCT/P to implant is not removing an HCT/P and then implanting “such HCT/P,” even accepting the district court’s finding that the individual cells that appear in both HCT/P’s “remain[] similar” and do not “significantly change.” 1-ER-16-17.

2. To advance their strained interpretation, defendants repeat the district court’s “surplusage” reasoning, which rests not on the same surgical procedure exception that is at issue, 21 C.F.R. § 1271.15(b), but rather on the general definition of an HCT/P in 21 C.F.R. § 1271.3(d) that is applicable throughout the provisions governing regulation of HCT/P’s. *See* Br. 63-64. But defendants have no answer to the point that even if the word “cell” in that general definition served no function for purposes of the same surgical procedure exception, inclusion of that term in this broadly applicable definition would not be surplusage because it would operate throughout the regulatory scheme. *See* Gov. Br. 35. That should be the end of this argument.

Defendants are also wrong to lean on (Br. 63-64) the district court’s statement that “[c]ells can only be removed from a patient along with larger systems, such as the tissues or organs that they comprise.” 1-ER-16. There can be no serious question, as

an expert witness testified, that doctors can remove human egg cells, or oocytes. Gov. Br. 35; 6-ER-767. That expert's testimony did not "contradict[]" her deposition, Br. 64; she simply "could not think of an example" when asked at a deposition and then had an answer at her fingertips when asked at trial. 6-ER-767. And the regulations could also reasonably allow for the possibility that over time scientists will develop a greater ability to extract cells in isolation. But again, because the definition of HCT/P is not simply limited to the one subsection at issue in this case, those debates are beside the point.

Defendants' response to the more dire surplusage issues that their own interpretation creates shows the implausibility of their approach. As pointed out in the opening brief, "[h]uman tissues are composed of cells, so if the relevant unit of analysis were the cell, the reference to tissues would be unnecessary." Gov. Br. 35-36. Defendants respond by citing the district court's conclusion that the relevant HCT/P is the one that the relevant procedure "target[s]." Br. 65 (quoting 1-ER-32). It is not clear why this point solves the superfluity problem; any procedure that targets a tissue could equally be described as targeting the component cells. But it does illustrate the self-defeating nature of defendants' interpretation: the fact that a procedure removes an HCT/P with no intention of implanting it into the patient is, on defendants' view, an affirmative reason to ignore that HCT/P in performing the analysis, rather than an indication that the procedure does not remove an HCT/P and implant "such HCT/P."

3. Defendants also disregard the context, structure, history, and purpose of the same surgical procedure exception. *See* Gov. Br. 28-30, 33-34. They do not even address the argument that reading the same surgical procedure exception to apply despite significant manipulation of the HCT/P that was removed would create a stark contrast with the other complete exceptions from regulation, which do not apply where establishments significantly manipulate an HCT/P and then implant it into a patient. *See* Gov. Br. 29-30.

As for the point (Gov. Br. 29) that defendants’ significant manipulation of adipose tissue would render them ineligible for even the lower tier of regulation in 21 C.F.R. § 1271.10, their primary answer is that the same surgical procedure exception does not use the term “minimally manipulated.” Br. 66-67. But the government’s argument is not that the Court should “graft” the minimally manipulated requirement onto the same surgical procedure exception. Br. 66. Rather, the Court should “interpret” the same surgical procedure exception—and, in particular, the textual requirement that an establishment remove an HCT/P and return “such” HCT/P, 21 C.F.R. § 1271.15(b)—“in light of the overall . . . regulatory scheme,” *Safari Club Int’l v. Haaland*, 31 F.4th 1157, 1171 (9th Cir. 2022). Here, that is a “tiered, risk-based approach to regulating HCT/P’s,” 66 Fed. Reg. 5447, 5449 (Jan. 19, 2001), in which HCT/P’s may be subject to a lower tier of regulation only if they are, among other things, “minimally manipulated,” 21 C.F.R. § 1271.10(a)(1); *see id.* § 1271.3(f). Defendants’ suggestion that some HCT/P’s can be ineligible for a lower tier of

regulation because they are not minimally manipulated but can nonetheless be excepted from regulation altogether would be anomalous. And defendants' contention (Br. 66-67) that they would satisfy the "minimally manipulated" requirement because each individual cell is not manipulated further illustrates their refusal to apply the regulatory scheme to the HCT/P's that they actually remove (adipose tissue) and implant (SVF). *See also* Gov. Br. 33-34 (discussing the regulatory scheme's distinction between "tissues" and "cells").

Defendants' response (*e.g.*, Br. 56-58, 67-68) that the regulatory scheme is concerned only with "communicable disease" is mistaken. As discussed in the preamble on which defendants rely, FDA "planned to issue new regulations under the communicable disease provisions of the Public Health Service Act," and "[s]ome [HCT/P's] would be regulated only under these new regulations, while other [HCT/P's] would also be regulated as drugs, devices, and/or biological drugs." 66 Fed. Reg. at 5448. This case is about whether the HCT/P's at issue here should be regulated as drugs, devices, and/or biological drugs under the FDCA. It would be nonsensical to make that determination based only on concerns about communicable disease, and FDA never purported to do so.

To the contrary, the entire point of the tiered regulatory structure for HCT/P's is to establish different tiers of regulations "commensurate with the public health risks presented." 66 Fed. Reg. at 5447. Since the beginning, FDA has made clear that it sought to except from regulation those activities where the "safety and effectiveness

risks” would be no different than the risks “typically associated with surgery,” 1997 Proposed Approach 12, and that FDA would continue to regulate “[c]ells and tissues that were manipulated extensively,” *id.* at 7. Defendants entirely disregard concerns about efficacy, *i.e.*, whether defendants can manufacture a new substance and make claims about the substance’s medical use without demonstrating effectiveness. *See, e.g.*, FDA, *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use* 3 (July 2020), <https://perma.cc/66AY-GJ43> (explaining that the “public health” includes “clinical safety and effectiveness”); *see also* 66 Fed. Reg. at 5459 (explaining that “HCT/P’s that rely on living cells for their primary function . . . raise clinical safety and effectiveness concerns”). And while defendants are correct that autologous use (from the same body) and use during a single extended procedure mitigates certain infection risks, *see* Br. 57, FDA has also identified various ways that, even in that context, extensive processing can create a substance that is unsafe and can itself risk contamination. *See, e.g.*, 1997 Proposed Approach 15 (explaining that “[i]mproper handling can alter or destroy the integrity or function of cells or tissues” or “allow cells or tissues to become contaminated,” and “inadequately-controlled processing can alter or destroy the integrity or function of cells or tissues”).

Defendants err when they urge (Br. 59-60) that because the district court did not find that defendants’ treatments pose “significant risks,” the FDA regulations should be read as excepting them from regulation. Eligibility for the exception is based upon the exception’s terms, not on the extent of the risk as measured by a district court.

Cf. Article of Drug Bacto-Unidisk, 394 U.S. at 791-792 (explaining that courts should not “substitute their judgment” or “second-guess” FDA’s judgment by “determining” for themselves whether regulation of a given product is “necessary” from a “public health” or “medical viewpoint”). The whole point of the tiered framework is that unless defendants’ activities fit into defined categories that authorize reduced regulation, *see* 21 C.F.R. § 1271.10(a), or entirely except establishments from regulation, *see id.* § 1271.15—then FDA, the expert agency, will assess safety and efficacy in the context of the FDCA’s overall regulatory scheme.

B. In all events, even if the same surgical procedure exception were considered to be ambiguous, FDA’s interpretation would be entitled to deference under *Kisor v. Wilkie*, 139 S. Ct. 2400 (2019), and *Auer v. Robbins*, 519 U.S. 452 (1997). *See* Gov. Br. 37-41. Defendants’ response largely claims that their view is not only right but “unambiguous[ly]” so, Br. 27, 50, and that FDA’s official, considered, and expert view is “unreasonable.” Br. 70. For the reasons just discussed, even were there any genuine debate about whether removing one HCT/P and implanting another HCT/P satisfies the terms of the exception, FDA’s position is a reasonable one.

Defendants fundamentally misunderstand the doctrine when they assert that FDA’s view is not “authoritative” because FDA’s guidance document clarifies that it “does not establish any rights for any person and is not binding on FDA or the public.” Br. 70. If the guidance document were binding, there would be no need for deference to its interpretation of the regulation; the court could just apply the guidance

document's binding terms themselves. The Supreme Court did not create a doctrine of deference that applies only when it is unnecessary.

Defendants' citation to *Kisor* confirms the point. There, the Supreme Court contrasted an "agency's 'authoritative' or 'official position,'" with a "more ad hoc statement not reflecting the agency's views." *Kisor*, 139 S. Ct. at 2416. The Court cited with approval various ways that an agency can communicate its "'authoritative' or 'official' position," *id.*, that do not also carry "binding force," Br. 70. The Court explained that, "[o]f course, the requirement of 'authoritative' action must recognize a reality of bureaucratic life" and need not "come[] from" or "even" be "in the name of, the Secretary or his chief advisers." *Kisor*, 139 S. Ct. at 2416. As an example, the Court pointed to "official staff memoranda that were published in the Federal Register" and "never approved by the agency head," *id.* (quotation marks omitted)—something that does not normally establish formal rights or bind the public. The Court clarified that it was carving out situations where an agency position does not "emanate from those actors" or "us[e] those vehicles" that are "understood to make authoritative policy in the relevant context." *Id.* The Court cited as examples a "speech of a mid-level official," an "informal memorandum recounting a telephone conversation between employees," and a guide that the "agency had itself disclaimed . . . as authoritative." *Id.* at 2416-2417 (quotation marks omitted).

The guidance here bears no resemblance to those examples. As explained (Gov. Br. 39-40, 40-41), FDA has established practices for drafting and finalizing

guidance, *see* 21 C.F.R. § 10.115, followed those practices, and has even posted the 2017 Guidance on a website that “lists all *official* FDA Guidance Documents,” FDA, *Search for FDA Guidance Documents*, <https://perma.cc/9VCK-8YBK> (emphasis added). FDA does so pursuant to a statute that directs the Secretary of Health and Human Services to “develop guidance documents” that “present the views of the Secretary” on matters under FDA’s jurisdiction, even though they do not “create or confer rights for or on any person.” 21 U.S.C. § 371(h)(1)(A). This guidance represents FDA’s “authoritative” and “official position.” *Kisor*, 139 S. Ct. at 2416. Defendants’ reliance on the Seventh Circuit’s decision in *Exelon Generation Co. v. Local 15, International Brotherhood of Electrical Workers*, 676 F.3d 566, 577 (7th Cir. 2012), is misplaced: there, the regulations themselves discouraged reliance on guidance documents other than those issued by the General Counsel. *See id.* (citing 10 C.F.R. § 73.3). For the reasons stated above, the case cannot stand—even in the Seventh Circuit—for the proposition that guidance documents must be binding to be entitled to *Kisor* deference.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be vacated and the case should be remanded.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limit of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 6,554 words. This brief also complies with the typeface and type-style requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) because it was prepared using Word for Microsoft 365 in Garamond 14-point font, a proportionally spaced typeface.

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